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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
OSTRUP, CLINTON T	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/091,061	LEE, FRANCIS Y.F.	
	Examiner	Art Unit	
	Clinton Ostrup	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *36-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35 and 71-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *36-70* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-75 are pending in this application.

Priority

Priority to Provision U.S. Application Number 60/275,801, filed March 14, 2001, and Provision U.S. Application Number 60/316,395, filed August 31, 2001, has been acknowledged.

Election/Restrictions

Applicant's election with traverse of Group 1, claims 1-35 and 71-75 in Paper No. 4 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Applicants election of the compound of formula I, Compound I, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione, on page 17 of the specification, and the antiproliferative agent capecitabine is acknowledged. Claims 1-35 and 71-75 will be read as comprising the elected compound and antiproliferative agent for search purposes until indication of allowable subject matter, at which time the search and the ultimate allowance of a generic claim will encompass all additional species within the scope of the allowed genus.

Claims 36-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 4.

35 USC § 112, First Paragraph-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 and 71-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of paclitaxel-resistant cancerous solid and refractory tumors, does not reasonably provide enablement for the treatment of any and all proliferative diseases in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

1. The nature of the invention, state of the prior art, relative skill of those in the art, the predictability of the art

The claimed invention relates to the treatment of proliferative diseases in general.

The relative skill of those in the art is generally that of a PHD candidate or PHD.

USP 5,919,816 represents a standard publication in the art and as such is directed to those having ordinary skill in the art.

USP 5,919,816 demonstrates the unpredictability of the claimed subject matter.

For example see column 1, lines 35-65, which teaches that the mechanisms by which anticancer drugs work are not well understood. Given this, the skilled artisan will appreciate that results obtained with a given agent for a particular cancer type (i.e. pancreatic cancer), which would be treated via different mechanisms, in an *a priori* manner. See: also the various case law which supports the assertion that cancer treatment across tissue types is unpredictable, e.g. Ex parte Timmis, 123 USPQ 581 (1959) and In re Butting, 163 USPQ 689 (1969).

Given the above facts, it is clear that the art to which the instant invention relates involves a relatively high degree of unpredictability.

2. The breadth of the claims

Claims 1-4, 7-23, 26-35, and 71-75 are very broad and inclusive of any and all proliferative diseases, including cancer. Claims 5-6 and 24-25 are broad and including of any and all solid or refractory tumors

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for treating specific types of proliferative disease, other that paclitaxel-resistant tumors, which are the only in vivo cell lines treated in the working examples. See: pages 57-69.

4. The quantity of experimentation necessary

Applicant fails to provide guidance and information sufficient to allow the skilled artisan to ascertain which specific proliferative diseases and cancers types, known or to be discovered, can reasonably be treated with the claimed agents of formula I, or any pharmaceutically acceptable salts thereof and any hydrates, solvates or geometrical and stereo isomers thereof, in combination with an anti-proliferative agent without resorting to undue experimentation. Testing would have to be conducted on each

cancer type, with no expectation of success for the treatment of any particular cancer other than paclitaxel-resistant tumors being present.

35 USC § 112, Second Paragraph-Indefiniteness Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-35 and 71-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation proliferative diseases, and the claim also recites cancer, which is the narrower statement of the range/limitation.

Claim 2 recites the limitation "the Formula I compound", however, there is insufficient antecedent basis for this limitation in the claim. There is antecedent basis for "the compound of formula I" and the examiner respectfully requests applicant be consistent in his terminology as well as his capitalization, as formula I is not a tradename, or a proper name, and should not be capitalized in the claims.

Claims 3-4, 30-31 are rejected for reasons analogous to those of claim 2 above.

Claims 9-11 are rejected because they recite "the Compound of Formula I" however there is insufficient antecedent basis for this limitation in the claims. There is however antecedent basis for "the compound of formula I."

Claims 12-16 are rejected because they recite "said compound of Formula I" however there is insufficient antecedent basis for this limitation in the claims. There is however antecedent basis for "said compound of formula I."

Claim 20 is rejected for reasons analogous to those of claim 2 above.

Claim 21 is rejected for reasons analogous to those of claim 12-16 above.

Claims 22 and 71-72 are rejected for reasons analogous to those of claim 9-11 above.

Claims 23 and 27 are rejected for reasons analogous to those of claim 12-16 above.

Any remaining claims are rejected as depending on indefinite base claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-35 and 71-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al., WO 99/02514 and further in view of Saeki et al., Mechanism and Possible Biochemical Modulation of Capecitabine (Xeloda), a Newly Generated Oral Fluoropyrimidine.

Vite et al teach, as an example, the specific compound elected by applicant, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione for the treatment of proliferative diseases including cancer. See: page 48, Example 3 and page 8 – page 11, Use and Utility. Vite et al teach that the compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments and describe cytotoxic drug combination wherein the second drug chosen acts in a different phase of the cell cycle than the present compounds are especially useful. See: page 10, line 10 – page 11, line 13.

Although the primary reference teaches the specific elected compound elected by applicant, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione for the treatment of proliferative diseases including cancer, the primary reference does not specifically teach the specific elected antiproliferative agent capecitabine.

Saeki et al. teach capecitabine (Xeloda; N-[1-(5-deoxy-b-D-ribofuranosyl)-5-fluoro-1, 2-dihydro-2-oxo-4-pyrimidyl]-n-penyl carbamate), was generated to decrease the incidence of GI toxicity and to increase the efficacy. The secondary reference teaches that capecitabine was designed as a prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is clinically used for gastric, breast and colorectal cancer patients undergoing single or combination chemotherapy. Saeki et al. teach capecitabine is converted to 5'-DFUR by either human carboxyestelase or cytidine deaminase, which are mainly localized in human liver and 5'-DFUR is converted to the active form of 5-FU by thymidine phosphorylase (dThdPase) in human tumors and the expression of dThdPase is higher in malignant tumors than in noninvolved normal tissues.

Thus, the secondary reference teaches that a high concentration of either 5'-DFUR or 5-FU in malignant tumors may be obtained by oral administration of capecitabine. Saeki et al teach that in vivo studies have shown synergistic or additive effects of capecitabine combined with anti-cancer agents such as, (Taxanes, Mitomycin C or cyclophosphamide), cytokines, growth factors and hormonal agents.

Finally, the secondary reference teaches that capecitabine may be biochemically modulated by those agents in vivo and in the results of an early phase II study on breast cancer patients in Japan, a high efficacy rate and low toxicity has been observed and describes capecitabine as one of the most promising orally administered 5-FU analogs. See: abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the compositions comprising [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione in combination with known anti-cancer and cytotoxic agents as taught by Vite et al. by using the well-known, widely used, orally administered anti-cancer agent, capecitabine, which has been shown to exhibit synergistic or additive effects, when combined with other anti-cancer agents and has a high efficacy rate and low toxicity when used in humans, as taught by Saeki et al. It would have been obvious to combine [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*, 16S*]] –7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione with capecitabine in a composition for the treatment of proliferative diseases, such as cancer, because of the reasonable expectation of obtaining a cancer treating composition and method of using same, which would exhibit synergistic or additive effects, have a high efficacy rate, low toxicity, and be easily administered.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (703) 308-3627. The examiner can normally be reached on 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Clinton Ostrup
Examiner
Art Unit 1614

Frederick Krass
Primary Examiner
Art Unit 1614

August 8, 2003